

Isolated limb perfusion (ILP) in surgical oncology

For which patient how and when

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Isolated limb perfusion (ILP) is a limb salvage procedure for inoperable limb melanoma with local in transit metastasis, and in selected cases for sarcomas as well. It allows to avoid amputation, improve dramatically local conditions and quality of life but does not increase global survival. The advanced concept applied in the CHUV is the combination of local chemotherapy with Tumour Necrosis Factor (TNF) and hyperthermia to increase local drug uptake and improve local complete response.

The ILP concept was developed by Creech, Ryan and Krementz in 1957¹. The idea was to perfuse local chemotherapy in a limb only, controlled by a tourniquet, with the main benefit of up to 10 times the maximum systemic tolerated chemotherapy doses, applied selectively to the limb without systemic toxicity². Many experiences and reviews have assessed the indications for melanoma and soft tissue sarcoma patients². Interestingly, ILP was developed in Europe mainly, where the adjunct of TNF demonstrated a significant improvement in efficacy². Despite many trials, TNF is still not FDA approved nor licensed in USA.

Due to high systemic toxicity, TNF management makes strict conditions in order to assess the risk of systemic contamination mandatory, and is to be performed with a special accredited multidisciplinary team including Surgical Oncology, Nuclear Medicine, Medical Oncology, sarcoma and melanoma teams as well as an Intensive Care Unit. There are currently about 40 certified centres performing ILPs in Europe, two in Switzerland: CHUV in Lausanne since 1990 and more recently the University Hospital of Basel.

Several agents have been tested for ILP but **melfhalan** is more commonly used. As single agent complete response (CR) is observed in about 50% melanoma patient with in transit limb metastases. Other agents like cisplatin and carboplatin have been applied but with higher local toxicity^{3,4}. Another derived technique was promoted by Thompson as Isolated Limb Infusion (ILI), with canulation through a contralateral intravascular route⁵. Fotemustin ILI after melfhalan failure, was used in combination with systemic dacarbazine⁶. ILI is however limited to the lower limb and is not suitable to treat disease up to the groin. Recombinant Tumour Necrosis Factor (**TNF- α** , Tasonerminum) is a proapoptotic molecule for angiogenic endothelial cells of tumours⁷, which induces vasoplegia increasing drug uptake and which has synergy with Interferon gamma. Combination of melfhalan with TNF increases CR up to 80-90%. Mild hyperthermia (40-41,5°C) is an additional factor

to further increase local effect of melfhalan. For sarcoma however, even if the association of melfhalan with TNF is more effective than melfhalan alone, CR is observed in 18% only⁸.

Indications

Melanoma: The major indication is **in transit metastases in melanoma patients** where surgical resection is not feasible (fig. 1). A large multicentric randomized trial showed that prophylactic ILP following curative melanoma surgery could increase disease-free interval for loco-regional recurrence, but offer no significant impact on distant metastases and overall survival⁹.

Non-resectable sarcomas: in soft tissue sarcoma limb-sparing surgery combined with external beam radiotherapy is feasible in up to 90% of patients¹⁰. Amputation does not improve survival, which is conditioned by size, grade and distant metastasis. ILP in this setting may be used as neo-adjuvant therapy in order to perform a safe RO resection (fig. 2) or as exclusive palliative therapy¹¹.

Miscellaneous: squamous cell carcinoma and Merkel cell carcinoma¹², desmoid tumours¹³ and T-cell lymphoma¹⁴.

Quality of life is obviously improved in tumour patients who can preserve their diseased limb¹⁵, even if survival will not be prolonged by the ILP procedure. For this reason, limited distant metastases is not a contraindication for ILP. After ILP about 50% melanoma patients will recur. A second (and third) ILP can be performed with more than 60% CR¹⁶. Sequential scheduled melfhalan ILP cumulates toxicity and is no more indicated. Age (>75) is not a contraindication: results are similar when compared with younger patients¹⁷.

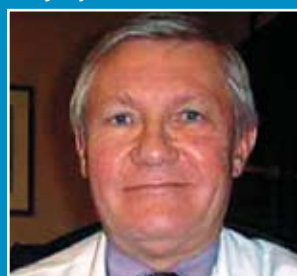
Surgical technique for ILP

Patients are selected in multidisciplinary sarcoma or melanoma tumour boards. For upper limbs, vascular canulation is either subclavian or axillary and for lower limbs is either iliac or femoral. A simultaneous radical lymph node dissection is performed according to the vascular access. In melanoma patients pelvic metastatic lymph node dissection may be beneficial, when distant disease is not observed¹⁸. In sarcomas lymph node metastasis is rare: overall less than 5%^{19,20} but related to histology (0,6% in undifferentiated sarcoma and around 20% in epithelioid sarcoma and rhabdomyosarcoma²⁰). Metastatic lymph nodes have a poor prognosis when associated with distant metastatic disease²¹.

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The procedure is performed on a limb isolated by a tourniquet (applied at the root of the limb) with extracorporeal circulation. Potential systemic leaks in the system are checked with technecium 99 labelled albumin. We use fluorescein and Wood lamp to assess the skin territory perfused. Sequential chemotherapy with TNF (plus INF for melanoma) and melphalan are perfused as soon as hyperthermia $> 38,0^{\circ}\text{C}$ is reached. In some centre compartmental tissue pressure is monitored²² in order to detect compartmental syndrome. The entire procedure lasts about 5 hours. After one or two days of recovery in the intensive care unit the patient starts rehabilitation. Mean hospital stay is 7-10 days, but full recovery necessitates assistance and physiotherapy up to 3 months.

Results and toxicity

For unresectable melanoma the main endpoint is limb salvage and quality of life. Because ILP remains a regional therapy overall survival will not be prolonged². ILP as exclusive treatment has 45-90% CR and a limb salvage rate up to 96%^{2,23}. In a series of 15 nonmelanoma skin tumours CR was obtained in 60% and limb saved in 80% of patients¹². In sarcoma patients the objective response (CR + partial) is 81-91% with limb salvage rate of 81-90%^{2,8}. In the CHUV in Lausanne we performed 255 ILP in 211 patients between 1990 and 2008. One ILP was performed once in 170 patients, twice in 38 and three times in 3 patients. Indications were in transit metastatic melanoma in 197, soft tissue sarcoma in 55, epidermoid carcinoma in 2 and Merkel cell tumour in one patient. Sarcoma patients were recently reviewed²⁴ showing 25% CR, resection of tumour remnants was performed in 65% and final amputation rate was 24% with a mean follow-up of 38,9 months (4-159).

Severe toxicity may include vasoplegia and shock, myelotoxicity, heart, liver, kidney and lung failures. Limb toxicity includes skin burns, rhabdomyolysis, neurotoxicity and rare septic necrosis leading to amputation. Post-ILP Creatinine Kinase monitoring may help detecting patients who may need fasciotomy, which is rarely necessary and performed²⁵.

Conclusion

ILP is a challenging therapy to be performed in specialized centres with multidisciplinary teams. As a loco-regional therapy ILP is important as limb sparing surgery for melanoma and soft tissue sarcoma patients. Other chemotherapy agents and specially the optimal TNF doses²⁶ are still in investigation.



Fig. 1. Melanoma patient. A 71 year-old woman was operated on for a Breslow 3mm melanoma of the right ankle followed 10 months later by a first ILP (TNF, INF and melphalan) for rapidly growing in transit metastases. Eight out of 13 ilio-obturator lymph nodes were metastatic. No objective response was observed. Metastatic skin nodules progressed with local infection. A second ILP was planned 10 months later with one-week preparation (antibiotics and local disinfection). A. One week before ILP. B. One week after ILP. C. Five weeks after ILP.

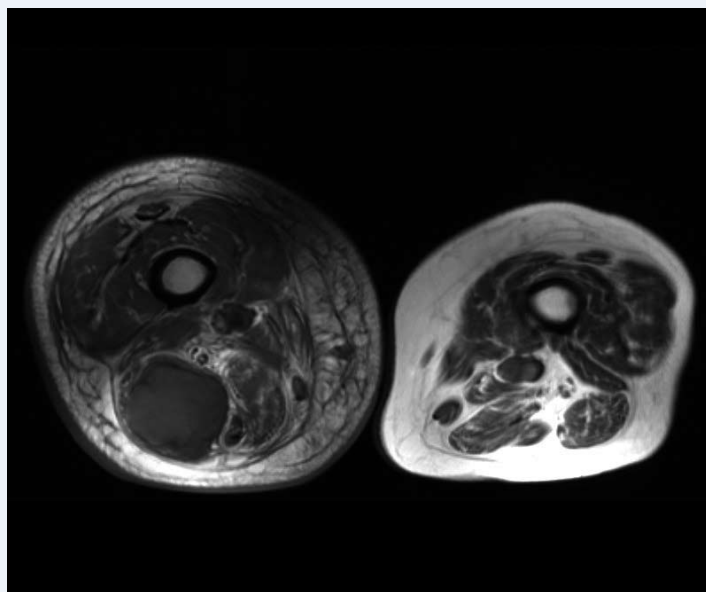


Fig. 2. Sarcoma patient. A 75 year-old man presented with a deep bulky sarcoma of the right thigh in the posterior compartment adjacent to the neuro-vascular bundle. Because of the risk of an R2 resection, a neoadjuvant ILP was planned. Ilio-obturator dissection revealed no lymph node metastasis (0/11). MRI (T1) at 2 and 4 months showed about 80% necrosis. Recovery was slow due to severe lymphoedema. Five months later a wide safe RO resection sparing sciatic nerve demonstrated a liposarcoma with 100% necrosis in the undifferentiated component and living tissues in the grade I liposarcoma area. Recovery was uneventful.

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